Received: 4 January 2018 | Revised: 8 February 2018 | Accepted: 28 February 2018

DOI: 10.1111/chd.12606

STATE OF THE ART ARTICLE

WILEY Congenital Heart Disease

Pulmonary hypertension: Barrier or just a bump in the road in transplanting adults with congenital heart disease

Jonathan N. Menachem MD[1] | Edo Y. Birati MD[2] | Payman Zamani MD[2] | Anjali T. Owens MD[2] | Pavan Atluri MD[3] | Christian A. Bermudez MD[3] | David Drajpuch NP[2] | Stephanie Fuller MD[4] | Yuli Y. Kim MD[2] | Christopher E. Mascio MD[4] | Vikram Palanivel MD[2] | J. Eduardo Rame MD[2] | Joyce Wald DO[2] | Michael A. Acker MD[3] | Jeremy A. Mazurek MD[2]

[1]Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[2]Division of Cardiovascular Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

[3]Division of Cardiothoracic Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

[4]Division of Cardiothoracic Surgery, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Correspondence
Jonathan Menachem, MD, Vanderbilt University Medical Center, Medical Center East, 1215 21st Avenue South, Nashville, TN 37232.
Email: jonathan.n.menachem@vanderbilt.edu

Abstract

Background: Heart failure (HF) is the leading cause of death in adults with congenital heart disease (ACHD). Identification of disease progression and timing of referral for advanced therapies is often delayed. However, increased awareness and understanding of ACHD and improvements in the approach to treatment have led to improved outcomes. Pulmonary hypertension (PH) is a common barrier to HT. In ACHD, the approach to PH and HT is quite complicated, given the anatomic heterogeneity and lower prevalence and experience. However, in some cases, PH is a result of elevated systemic filling pressures and low output.

Methods: We describe the approach used to successfully transplant an ACHD patient with severe pre-HT PH performing HT alone. We review the literature and describe the one patient's journey from primarily palliative, to a combined heart-lung transplant candidate, to successful HT patient.

Results: We discuss the methodology used to successfully transplant a patient, with significantly elevated pulmonary pressures and an initial pulmonary vascular resistance (PVR) > 13 Wood units.

Conclusions: There are a number of complexities associated with the ACHD population and it is of utmost importance to carefully identify the underlying hemodynamic milieu and inform the appropriate treatment course in order to have successful transplant outcomes.

KEYWORDS
adult congenital heart disease, pulmonary hypertension, transplantation, transposition

1 | INTRODUCTION

Heart failure (HF) is the leading cause of death in adults with congenital heart disease (ACHD), leading to an increasing number of referrals to transplantation centers for heart transplantation (HT).[1–3] Predicting progression from stable to advanced and/or decompensated HF in ACHD-related HF remains challenging. While several parameters including declining NYHA class, progressive ventricular dysfunction, elevated serum BNP[4,5] reduced peak oxygen uptake (VO2 max), and low BMI have each been associated with increased mortality, the specific thresholds to drive decisions regarding timing of advanced therapies referral are lacking. Despite this, more recently, increased awareness and understanding of ACHD and improvements in the approach to treatment have led to improved outcomes.[6–8]

Pulmonary hypertension (PH) is a common barrier to HT, especially in the ACHD population as the approach to PH and HT becomes more complicated in comparison to the overall population, given the anatomic heterogeneity and lower prevalence and experience. Currently, there are only four placebo-controlled trials for ACHD patients with PH.[9–11] While guidelines and evidence-based therapies exist for non-ACHD patients[12] the challenge in ACHD patients is the impact that the various anatomical alterations have on PH. It would be incorrect to

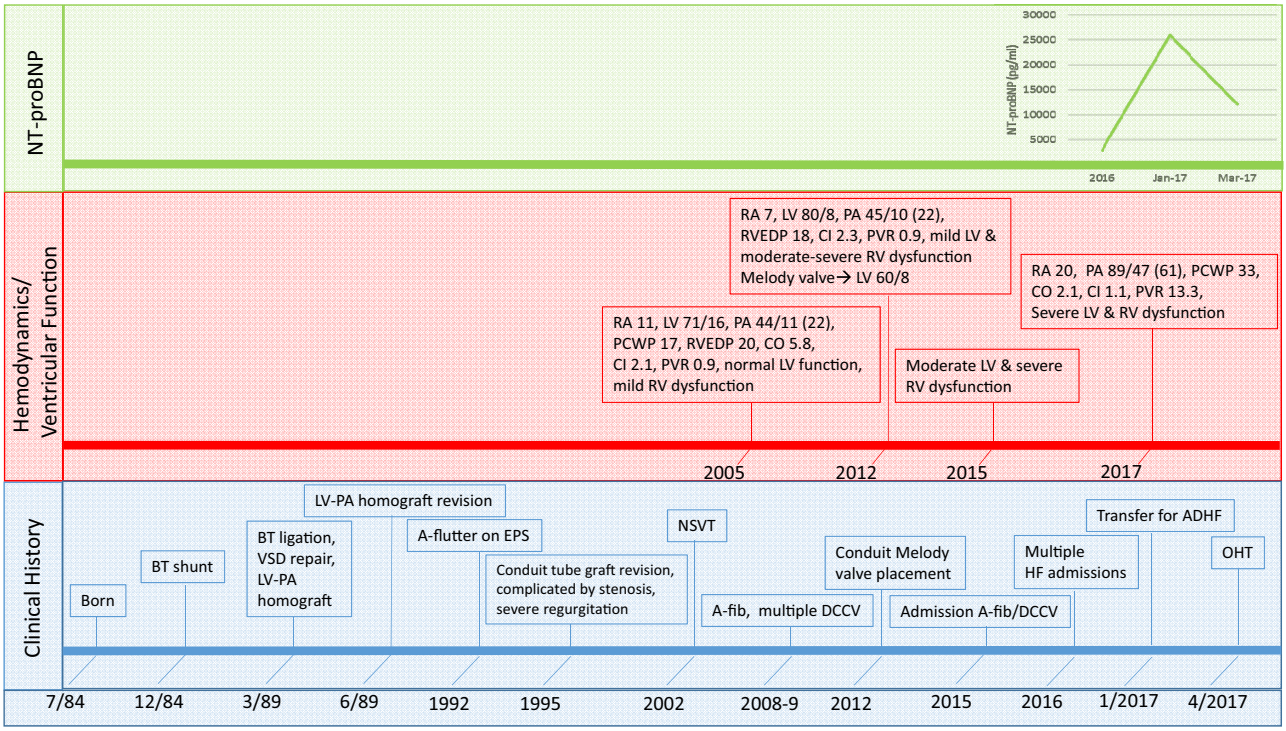

FIGURE 1 The patient's journey

assume that all PH that is associated with congenital heart disease (WHO Group 1.4.4) is the same.[13]

From 2010 to 2017, our center transplanted 23 ACHD patients—2 having with I-Transposition (I-TGA).[7] Due to the complexity of these patients, we review the literature and describe the important considerations of transplantation, using one I-TGA patient's journey from primarily palliative, to a combined heart-lung (HLTx) transplant candidate, to successful HT patient. We discuss the methodology used to successfully transplant a patient, with significantly elevated pulmonary pressures and an initial pulmonary vascular resistance (PVR) > 13 Wood units (WU). We focus our attention on the various options considered, the potential concerns for each, and our rationale behind proceeding with HT alone. We also describe the role PH played in the case of the lone mortality.

2 | CASE

The patient is a 32-year-old male with dextrocardia, {S,L,L} double-outlet RV with pulmonary stenosis, status post Blalock–Taussig (BT) shunt, biventricular repair and LV to PA conduit, left SVC to coronary sinus, and subsequent transcatheter pulmonary valve 5 years prior to coming to our hospital (Figure 1). Despite "no symptoms" while working tiling floors, he had warning signs of impending failure including atrial and ventricular arrhythmias, requiring cardioversions and a depressed cardiac index of 2.3 L/min/sqm on right heart catheterization (RHC) at the time of pulmonary valve intervention (Figure 1). In addition, his echocardiogram demonstrated moderate-to-severely decreased systemic RV function with moderate to severe tricuspid regurgitation. He was then lost to follow-up due to a lapse in insurance and next presented to an outside hospital 6 months prior with shortness of breath. His symptoms quickly resolved with IV diuretics and he was able to return to work. Within weeks he once again presented with significantly worsened exercise intolerance, dyspnea, fatigue, and orthopnea and was ultimately transferred to our institution.

On admission, the patient appeared stable but underwent a RHC which demonstrated elevated filling pressures with severely low cardiac output and significantly elevated PVR of > 13 WU (Table 1). The patient was placed on milrinone and the evaluation process for advanced HF therapies was initiated.

3 | COMMENT

3.1 | General points

Recognizing the progression from stable to advanced or decompensated HF in ACHD related HF is complicated and challenging as patients are often young and relatively well appearing. More important than any one single variable is the overall clinical picture with focus on repeat HF associated hospitalizations, increased frequency of arrhythmias, intolerance to HF pharmacologic therapies, or requirement of increased diuretic dosing.

Furthermore, despite many warning signs, the patient was in and out of care due to lapses in insurance. Unfortunately, issues with compliance are well documented in young adults with congenital heart disease and stem from a variety of factors including transitions in care, social pressures surrounding illness, and lack of mature decision making, among others.[14,15]

TABLE 1 Selected hemodynamics

Date	RAP (mm Hg)	PAP (mm Hg)	PCWP (mm Hg)	CO (L/min)/ CI (L/min/m^2)	DPG (mm Hg)	TPG (mm Hg)	PVR (WU)
Presentation	20	89/47 (61)	33	2.1/1.1	14	28	13.3
Day 2	13	81/39 (54)	31	2.4/1.4	8	23	9.6
Day 6 (baseline)	NA	90/47 (65)	40	2.1/1.2	7	25	11.9
Day 6 (nitroprusside 5 mcg/min)	NA	54/30 (40)	14	3.9/2.3	16	26	6.7
Day 26	5	56/24 (36)	23	3.8/2.2	1	13	3.4
Day 34	10	72/30 (46)	26	4.2/2.5	4	20	4.8
Day 37 (baseline)	21	83/32 (52)	33	3.7/2.1	−1	19	5.1
Day 37 (nitroprusside 7 mcg/min)	12	45/17 (32)	15	5.6/3.3	2	17	3.0
Day 41	12	75/31 (48)	29	5.5/3.1	2	19	3.8
Day 51	7	26/10 (14)	8	3.1/1.8	2	6	1.9
Day 74	4	39/22 (28)	22	3.4/2.0	0	6	1.8
Day 93	1	59/25 (35)	25	2.6/1.6	0	10	3.8
Day 100	2	36/13 (22)	16	4.2/2.5	−3	6	1.4
6-months post-HT	4	29/10 (17)	8	4.4/2.4	2	9	2

Abbreviations: RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; DPG, diastolic pulmonary gradient; TPG, transpulmonary gradient; PVR, pulmonary vascular resistance; WU, Wood units.

3.2 | Advanced HF therapeutic options

Our goal was to successfully transition the patient to the most appropriate and stable platform. We considered the options including, palliative milrinone, HT, ventricular assist device (VAD) as a bridge to HT alone and combined HLTx. Per ISHLT registry data, HLTx has significantly worse survival compared with HT alone,[16] with an average life expectancy of 3.3 years for HLTx vs 10.4 years for HT.[17] However, at this point it was unclear whether his PVR would be within acceptable range for HT alone.

3.3 | Assessment of pulmonary hypertension pre–heart transplantation

The assessment of PH and specifically the identification of "reversible" vs "fixed" disease has been the topic of study in the area of HT in general and of particular concern in ACHD patients. It has long been recognized that RV failure is a common occurrence after HT, with nearly 20% of early deaths attributed to the development of RV failure. This prompted the Stanford program in the late 1980s and early 1990s to identify hemodynamic parameters that would determine appropriateness of HT.[18] Data from this group divided patients by PVR (<2.5 WU and >2.5 WU) and their PVR and systemic blood pressure (SBP) response after nitroprusside administration. They identified a high risk group of those patients with nonreversible PVR or those with PVR reversal (<2.5 WU) *and* a drop in SBP <85 mm Hg. The low risk group comprised those with a PVR <2.5 WU at baseline or after nitroprusside *without* a decrease in SBP <85 mm Hg. The high risk group had significantly higher 3-month mortality (33%; 14% related to RV failure) compared with the low risk group (6%). Others have looked at the role of other agents including prostacyclins and nitric oxide in assessing response of PVR prior to HT. Data from Butler et al identified higher post-HT mortality in patients with a PASP >50 mm Hg pre-HT, even if the PVR reversed to ≤2.5 WU, as compared with those whose PASP was <30 mm Hg at baseline.[19] More recently, Tedford et al evaluated the prognostic role of the diastolic pulmonary artery pressure to pulmonary capillary wedge pressure gradient (DPG) to predict post-HT survival.[20] The DPG, as opposed to the TPG and PVR, is not affected by alterations in left atrial pressure or cardiac output and thus may be more indicative of true precapillary PH or pulmonary vascular disease. In this retrospective UNOS analysis, they found that an elevated DPG (using several DPG cut points and either an elevated TPG or PVR) did not predict post-HT survival, nor did an elevated TPG (>15 mm Hg) or an elevated PVR (>5 WU). Furthermore, one report has called into question the assumptions and benefits of the DPG noted above, with many calling for the consideration of several metrics (DPG, TPG, PVR, among others) to assess PH in the setting of left heart disease.[21,22]

Overall, these studies and the approach of the guidelines underscore the fact that one static measurement or reliance on one specific parameter to characterize the degree/type of PH prior to HT is inadequate, and that it requires serial monitoring, provocative maneuvers and an integration of several indices to better identify risk prior to HT.

Beyond this, specific issues exist in the ACHD population including the accuracy of measurement in congenital patients,[23] approved therapeutic options, as well as PVR levels in which a patient can successfully undergo HT. Assessment of PH in ACHD patients is made more challenging by the presence of complex anatomy, passive pulmonary blood flow, imbalanced flow to the right and left lung, and alternative sources of pulmonary blood flow in the form of collateral vessels. Studies in

these patients are inconsistent using both Wood units and TPG to drive decisions.[24] A recent UNOS analysis demonstrated no difference in outcomes when groups were dichotomized by pretransplant TPG <6 and >17.[25] While this study was limited by lack of hemodynamic data at the time of transplantation, it demonstrates the important point that PH in the ACHD population can often be safely managed through transplant.

Furthermore, while PH has most recently been described in the d-TGA status post atrial switch population as a prevalent (54.5%), late finding, that is largely post-capillary and not associated with RV dysfunction, the same may not be true for l-TGA patients.[26] In fact, there is little data describing the prevalence or mechanism of PH in l-TGA, with no data to help aid in PH assessment and decision in the context of consideration of advanced HF therapies.

The initial view of the treatment team was that the patient was severely decompensated with a component of significant pre- and post-capillary PH. We planned to assess the response of several metrics including cardiac output, pulmonary capillary wedge pressure, pulmonary pressures and by calculation, TPG, DPG, and PVR to inotropic support and diuresis. Given severe decompensation, we did not proceed initially with vasodilator challenge. We were hoping to achieve a degree of improvement in hemodynamics before reassessing with nitroprusside challenge to assess PH reversibility (Table 1), as discussed below.

3.4 | Mechanical support

As mentioned above, reversibility of PVR is key to determining candidacy for HT. Beyond medical optimization and provocation, the updated 2016 ISHLT guidelines recommend "if medical therapy fails to achieve acceptable hemodynamics and if the LV cannot be effectively unloaded with mechanical adjuncts, including an intraaortic balloon pump (IABP) and/or LVAD, it is reasonable to conclude that PH is irreversible."[27] Thus, temporary and durable mechanical support serves an important role in mitigating risk related to PH pre-HT. Several studies have demonstrated successful bridge to transplant with initial VAD support for reversal of PVR, with one study showing increased risk for early posttransplant mortality in those with elevated PVR pre-VAD.[28] Due to small sample sizes, this has yet to be replicated in congenital heart disease (CHD) patients.

Currently, VAD use remains limited in ACHD patients, despite favorable outcomes in a recent INTERMACS analysis.[29] In this study, while survival was similar between ACHD and non-ACHD patients, ACHD patients were three times more likely to undergo a biventricular assist device or total artificial heart. Furthermore, best practices remain in question regarding the treatment of congenital patients, as most of the data regarding mechanical support in systemic RV patients are single-center, small case series.[30,31] In fact, a total 37 reports describing 66 ACHD and teenage CHD patients with VADs were published from 1999 to early 2016 with the largest of these including seven patients.[32]

In this case, VAD was considered as a bridge to HT as a method to unload the systemic RV and reverse the PVR, however, the midline and anterior orientation of his systemic ventricle in the setting of his dextrocardia, would have required atrial cannulation. While this has been described, there was concern as to the durability of this approach for this patient.[31] Second, the echocardiogram demonstrated a severely dysfunctional subpulmonic LV. Unfortunately, there are limited data regarding the risk of subpulmonic LV failure. This uncertainty coupled with need for atrial cannulation made VAD a less desirable therapeutic option.

3.5 | Combined heart-lung transplantation vs heart transplant alone

In the absence of PVR reversibility, the discussion becomes one of palliative therapies vs HLTx. Unfortunately, HLTx is a high-risk surgery in which median survival is far worse than HT alone, as noted above. Additionally, between July 2015 and June 2016 there were only 12 HLTx completed in the US with only one center completing more than one.[33] Importantly, however, conditional median survival based on 1-year survival is significantly improved for HLTx overall (10 years), and is better in those with CHD who undergo HLTx (~12 years), though this is still worse than median conditional survival for HT alone (13 years).[16]

4 | CASE CONTINUED

With the above in mind, after initially considering palliative milrinone due to high surgical risk, with improvement of end-organ function and hemodynamics over 5 weeks, we briefly pursued listing for HLTx, converting to listing for HT alone 3 days later due to sustained hemodynamic improvements including reductions in TPG, DPG, and PVR (Table 1). The patient was initially listed UNOS status 1B for HT and then granted a UNOS status 1A exception.

5 | COMMENT

5.1 | Swan-guided therapy

Despite a lack of mortality data, indwelling RHC is guideline driven and can dramatically alter the therapeutic pathway in the outwardly deceiving phenotype of the ACHD patient.[34,35] Indwelling RHC within the pediatric population is less common due to size and activity level of children. However, in adults, RHC-guided therapy is standard of care with careful consideration of the risk of heart block in an l-TGA. As with non-CHD cases, the quality and usefulness of the information provided is related to appropriate preparation, which in these cases should involve the anatomical interpretation from the ACHD specialist.[36] Additionally, as is the case with any hemodynamic assessment, it is always important to ensure that the values obtained are as accurate as possible. Fortunately, in this case, the wedge pressure tracings were "clean" without evidence of v-waves or significant respirophasic variation, simplifying the assessment. As is standard in both our catheterization laboratory and cardiac care unit, we measure end-expiratory PCWP as it is the point where intrathoracic pressure is approximately equal to atmospheric pressure, and thus reflects transmural systemic ventricular filling pressure. In scenarios where significant v-waves or respirophasic variation is present, the end-expiratory wedge pressure

may be erroneous and we would assess hemodynamics using the computer-generated mean PCWP, though data in this regard are limited and controversial.[37,38]

For the duration of the admission prior to HT, RHC-guided therapies including inotropes, vasodilators, and diuretics were utilized, and the first notion of reversibility occurred on day 6 with a dramatic improvement in PCWP with nitroprusside infusion. Due to thrombocytopenia, milrinone was discontinued and intraortic ballon pump was not trialed, and the patient was treated with prolonged dobutamine and nitroprusside. The process of PVR reversal is not medication or dose dependent. Our approach was to allow for safely maximizing time on medical support to achieve sustained reversibility. It should be noted, that the patient was maintained on inotropic and IV afterload and diuretic therapies for nearly 6 weeks prior to listing for HT alone, and over 3 months from time of admission to HT. Furthermore, the patient was never initiated on pulmonary vasodilators (specifically sildenafil), as there was improvement in his pulmonary vascular parameters with maximal systemic unloading. While the use of sildenafil has been studied in HT candidates for the management of PH and RV failure pre- and post-HT, these studies are small and single-center in nature.[39,40] Unpublished data from our center suggests that there is a significantly increased risk of short-term mortality in those patients on high-dose sildenafil (>20 mg TID) compared with those on low-dose or no sildenafil prior to HT.

5.2 | Sensitization

Sensitization, the process by which preformed antibodies to human leukocyte antigens (HLA) are developed, remains an important barrier to HT. Patients with panel reactive antibodies (PRA) greater than 10% are considered sensitized. Sensitization risk factors include prior blood transfusions, pregnancies, homografts, tissue allografts, and mechanical circulatory support.[41] HT recipients with high degrees of sensitization have increased wait-list times and are at a higher risk of post-transplant rejection, cardiac transplant vasculopathy, graft failure, and mortality.[24,42–44] The waitlist mortality is even worse for ACHD patients, often complicated by sensitization due to prior exposure to blood products.[45] The patient's calculated PRA prior was 48% in the setting of an A2 antigen, which required virtual crossmatch.

Desensitization was deemed too high risk, especially in the setting of a long hospitalization due to infectious risk. Desensitization can allow patients to undergo HT with a negative prospective donor-specific crossmatch. Surprisingly, equivalent 5-year survival has been reported in sensitized patients undergoing HT with and without prior desensitization.[46] These findings suggest desensitization increases the chance of sensitized patients proceeding to HT with a negative crossmatch but without clear evidence for improved long-term survival.

5.3 | Listing status

Previously, a UNOS analysis from 2005 to 2009 demonstrated that 36% of patients with ACHD were listed 1A/B in comparison to 55% of patients without ACHD.[47] Once listed, ACHD patients spend a longer time on the waiting list due to listing as less urgent, sensitization, and the common need for non–lung donors to enable vascular reconstruction.[1,47] Since 1996, the number of ACHD patients listed status 2 has remained constant whereas for non-ACHD patients this percentage has fallen likely due to an increase in the number of non-ACHD patients being upgraded to status 1.[48] Changes in the organ allocation policies, including a provision that patients with a VAD be listed as status 1B and receive 30 days of discriminatory 1A time as well as 1A status for VAD complications, leaves ACHD patients at a significant disadvantage.

Due to the current listing policies, it is quite common for ACHD patients to require listing by exception in order to attain 1A status. In fact, fourteen percent of exemptions between 2009 and 2011 were for patients with ACHD.[49] As noted above, the patient was listed status 1B and then granted a 1A exception in the setting of thrombocytopenia and episodes of atrial and ventricular arrhythmia precluding augmentation of inotropic support.

6 | CASE CONTINUED

On hospital day #102, an appropriate organ became available for the patient. The patient was taken to the operating room with HT performed jointly by an adult transplant surgeon and a congenital surgeon. In addition to the transplant, the patient had dextrocardia and required a conduit to re-anastomose his persistent left sided SVC. The native main PA orifice was closed with bovine pericardial patch, and a new more leftward displaced and traditionally oriented opening was created in the pulmonary artery. A PTFE graft was anastomosed to the left SVC in an end-to-end fashion. The total ischemic time was 195 minutes.

7 | COMMENT

7.1 | Perioperative management

Excellent outcomes have been reported with congenital heart and adult HT surgeons working in collaboration, not only at the time of surgery but also in the assessment and planning stages.[7,8] ACHD patients present additional anatomic challenges, and the survival of patients undergoing cardiac transplant with complex CHD was shown to be significantly impacted by the need for pulmonary artery reconstruction at the time of transplantation.[50] As such, current guidelines recommend all ACHD patients undergo transplantation in high volume centers with combined expertise in CHD and HT.[27]

In addition, to a successful surgical operation, outcomes remain dependent on precise perioperative management. Graft failure secondary to elevated PVR, allosensitization, longer donor organ ischemic times, and post-operative bleeding are the most likely cause of death in ACHD transplants and is the driver for the mortality difference between ACHD and noncongenital transplants.[6]

As described, our experience has been similar to what has been described in the literature, and for that reason we closely monitored and prepared for the possibility of right HF in the l-TGA patient. As

such, we moved slowly in regards to extubation (postoperative day #2) to prevent hypoxia-induced vasoconstriction, continued invasive hemodynamic monitoring, and used inhaled nitric oxide with transition to low dose sildenafil (20 mg three times daily).

Lastly, it is important to understand the impact the patient's prior anatomy and surgeries have on care even after transplantation. This patient's prior BT shunt caused a diminished pulse in his right arm and perceived hypotension. This led to the brief use of pressors, prior to recognition and sole use of his left arm for blood pressure measurement.

8 | CASE CONTINUED

The patient made steady progress, and on postoperative day #20, 4 months after admission, the patient was deemed medically stable for discharge. At the time of this submission, 1 year to the time of presentation, the patient is doing very well with normal hemodynamics off sildenafil (Table 1) and is leading a happy and healthy life with his wife and two young children.

9 | CONCLUSION

This case highlights the complexities associated with the ACHD population and importance of carefully identifying the underlying hemodynamic milieu to inform the appropriate treatment course. While this particular patient initially had severe PH due to elevated pulsatile load in the setting of severe systemic congestion and low output, we ultimately proceeded with HT alone as we were encouraged by an improvement in hemodynamics by effectively optimizing systemic unloading and contractility without the need for PH therapy.

ACKNOWLEDGMENTS

We would like to acknowledge and thank the following people: Christopher Domenico, Pharm. D., Arieh Fox, MD, Lee Goldberg, MD, Nicole Hornsby, NP, Anthony Kaiser, RN, Rhondalyn McLean, MD, Monique Tanna, MD, and Lynda Tobin, NP.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Designed, drafted, revised and approved the final version: Dr. Menachem and Dr. Mazurek.

Designed, revised, and approved the final version: All other authors.

ORCID

Jonathan N. Menachem MD http://orcid.org/0000-0003-4787-1906

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How to cite this article: Menachem JN, Birati EY, Zamani P, et al. Pulmonary hypertension: Barrier or just a bump in the road in transplanting adults with congenital heart disease. *Congenital Heart Disease*. 2018;13:492–498. https://doi.org/10.1111/chd.12606